REMARKS

Claim 31 has been cancelled.

Claim 23 has been amended to recite "[a] process for decoupling production of a target fermentation product from biomass production in a fermentation medium comprising: (a) providing a recombinantly produced microorganism from the genus Bacillus that has been engineered to contain a polynucleotide sequence which encodes biosynthetic enzymes for said target fermentation product, (b) introducing a mutation causing a biotin auxotrophy into the microorganism to control biomass production and which does not compromise the ability of the microorganism to produce said target fermentation product, and (c) supplying the medium with an unlimited amount of substrates required for the production of said target fermentation product and with a limited amount of biotin complementing the auxotrophy; wherein said target fermentation product is ***riboflavin***." (Emphasis added). Support for this amendment is found in original claim 23 and in the specification at, for example, page 8, lines 1-2. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l).

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments respectfully is requested.

INTERVIEW SUMMARY

The Examiner is thanked for the courtesies extended during a telephonic Interview conducted with the undersigned on February 16, 2007. During the interview, the rejections under 35 USC § 112, first paragraph, were discussed. The Examiner agreed to review these rejections in light of the amendments presented above and

arguments presented below. In view of the remarks below, withdrawal of the rejections and allowance of the claims are respectfully requested.

§112, First Paragraph Rejections

1. Enablement

Claims 23-32 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. (Paper No. 20060922 at 2). In making the rejection, the Examiner concluded that the claims were not commensurate in scope with the specification, and, therefore, that it would require undue experimentation to practice the claimed invention. (*Id.* at 2-10). The crux of the rejection appears to lie with the Examiner's assertion that it would require undue experimentation to identify recombinantly produced microorganisms wherein the target fermentation product is other that riboflavin, *e.g.*, pantothenic acid, thiamin, folic acid, and pyridoxine, as claimed. (*Id.* at 9) ("... the specification does not provide sufficient teachings on the genes encoding biosynthetic enzymes for producing target fermentation product pantothenic acid, thiamin, folic acid, or pyridoxine ....).

Indeed, the Examiner conceded that the specification is enabled when the target fermentation product is riboflavin and the auxotrophy is for biotin:

> [T]he specification [is] ... enabling for a process for decoupling production of a specific target fermentation product (i.e., riboflavin) from biomass production in a fermentation medium ...." (*Id.* at 2-3).

With a view towards furthering prosecution, we agreed at the Interview to amend claim 23 so that it currently recites, *inter alia*, (1) that the recombinantly produced microorganism is a *Bacillus*, (2) that biotin is the specific auxotrophy, and (3) that riboflavin is the specific target fermentation product.

In this regard, we note that the genes involved in biotin biosynthesis are well known to those skilled in the art. In view of the disclosure in the specification and the general knowledge in the art, undue experimentation would ***not*** be required to generate mutants and test them for biotin auxotrophy. For example, the specification discloses that the mutation causing auxotrophic growth may be introduced using any convenient means, such as for example by "chemical and UV mutagenesis followed by screening or selection for a desired phenotype." (Specification, p. 8, lns. 16-19). Simple screens for confirming an auxotrophy are likewise disclosed in the specification:

> A microorganism that is an auxotroph for biotin is unable to grow without supplementation with biotin, *i.e.*, the substrate complementing the auxotroph. (*Id.*, p. 12, lns. 18-20).

Surely, such an assay was well within the skill of the art. And, specific exemplification of a process for decoupling production of riboflavin from biomass production with biotin auxotrophy is disclosed, including a description of how to make a specific biotin auxotroph. (*See*, *e.g.*, Specification, pp. 15-18; Examples 1-3; and Figs. 1-4).

Moreover, the level of knowledge and skill in this art is high. Indeed, the Examiner has confirmed this:

> The related art (references on pages 1-4 of the specification) teach recombinant production of riboflavin and genes involved in the riboflavin biosynthetic pathways; and the art contains many examples of required genes whose mutation is likely to cause auxotrophy (e.g., Dev et al. (1984), cited in IDS).

Thus, in view of the claim amendments, the clear disclosure in the specification of how to make biotin auxotrophs that produce riboflavin, and the acknowledged high degree of skill and knowledge in the art, we respectfully submit that the claims, as amended, are sufficiently enabled.

In view of the foregoing amendment and comments, we respectfully submit that very little real experimentation would be needed to practice the full scope of the claims. And, should any experimentation remain (we submit that none does), how to conduct that experimentation is described in the specification and would be simple, routine matter for someone skilled in this art given the specification. Indeed, even a "considerable amount" of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. MPEP § 2164.05 and *In re Wands*, 8 USPQ at 1404. Here, as discussed above, the specification provides ample guidance, for the process recited in currently amended claim 23. (*See, e.g.,* Specification at pages 12-18 and Examples 1-3). Also, as discussed with the Examiner, the genes involved in biotin biosynthesis are well known to those skilled in the art, and there would be no undue experimentation to generate such strains and test them for biotin auxotrophy in light of Applicants' disclosure and the knowledge in the art. (*See, e.g.,* Specification at page 12, lines 14-22 and Figures 3-4). In this regard, we note that the specification discloses in Example 1 construction of biotin auxotrophic Bacillus mutants. Accordingly, it is respectfully submitted that ample guidance is provided in the specification. Thus, for the reasons set forth above, the rejection should be withdrawn.

It is also well established that claims must be separately analyzed. *Ex parte Jochim*, 11 USPQ2d 561 (BPAI 1988). Here, the Examiner has not referred to any specific features of any of the dependent claims that are insufficiently enabled. To the contrary, the Examiner has simply posited, in conclusory fashion, that, with respect to claim 23, "[t]he specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." (Paper No. 20060922 at 3). Accordingly, it is respectfully submitted, for this additional reason, that the rejection should be withdrawn as to claims 24-32.

2. Written Description

Claims 23-32 have been rejected under 35 U.S.C. §112, first paragraph. (Paper No. 20060922 at 10-11). In making the rejection, the Examiner asserted that claims 23-32 "contain subject matter which was not described in specification ...." (*Id.* at 10). The Examiner further asserted that "the specification does not disclose a genus of variants for recombinantly produced microorganisms of bacillus that contain a polynucleotide sequence that encodes biosynthetic enzymes for a target fermentation product of pantothenic acid, thiamin, folk acid or pyridoxine, and biotin auxotrophy-causing polynucleotides." (*Id.* at 10-11). Just like the enablement rejection, the crux of this rejection appears to be the Examiner's contention that the specification does not disclose polynucleotide sequences that encode biosynthetic enzymes for a target fermenattion product other than riboflavin:

> Without guidance on the polynucleotide sequences that encode biosynthetic enzymes for a target fermentation product of pantothenic acid, thiamin, folic acid, or pyridoxine ... one skilled in the art would not know how to identify functional variants used in the claimed method. (*Id.* at 11).

With a view towards furthering prosecution, we agreed at the Interview to amend claim 23 so that it now recites, *inter alia*, (1) that the recombinantly produced microorganism is a *Bacillus*, (2) that biotin is the specific auxotrophy, and (3) that riboflavin is the specific target fermentation product.

As noted above, the Examiner has conceded that the art is well established in this area. Indeed, the Examiner has acknowledged that methods for making recombinant riboflavin were known, that the genes involved in the riboflavin biosynthetic pathway were known, and that methods for making auxotrophs were known.

> The related art ... teach recombinant production of riboflavin and genes involved in the riboflavin biosynthetic pathways; and the art contains many examples of required genes whose mutation is likely to cause auxotrophy .... (*Id.* at 5) (internal citations omitted).

Coupled to the already acknowledged high level of knowledge and skill in the art, the present specification discloses how to make mutations that may lead to auxotrophs (*see, e.g.,* Specification, p. 8, lns. 16-19), simple assays for confirming an auxotrophy (*Id.*, p. 12, lns. 18-20), and exemplification of the specific biotin auxotroph (*see, e.g.*, Specification, pp. 15-18; Examples 1-3; and Figs. 1-4). Indeed, the Examiner has acknowledged the description, in the specification, of an exemplification of biotin auxotroph, namely:

> [A] process for decoupling production of a target fermentation product from biomass production in a fermentation medium by introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO: 1 into *bacillus subtilis* RB50 containing multiple copies of the engineered *rib* operon pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations, which shows the product yield (i.e., the amount of riboflavin produced on the consumed glucose) is 33% higher in the decoupled process to the coupled process (see Examples 1-3) .... (Paper No. 20060922 at 10).

We also note that the specification also discloses how to identify *Bacillus* strains that would fall within the scope of amended claim 23 (and, therefore, within the

scope of dependent claims 24-32). The specification discloses, for example, at page 11, lines 17-20 the production rate of a microorganism carrying an auxotrophy; at page 12, lines 18-20 the specification discloses that a microorganism that is an auxotroph for biotin is unable to grow without supplementation with biotin (if the strain is a biotin-auxotroph); and at page 14, lines 8-11 the specification discloses an increase of 0.1% in the yield of the target fermentation product after engineering of the host microorganism. Also, the Examples disclose construction of biotin auxotrophic Bacillus mutants, continuous culture fermentations, and biomass and riboflavin production in coupled and decoupled processes. (*See* Examples 1-3). Therefore, there is sufficient information disclosed within the specification for one of skill to easily determine whether a strain would fall within the currently amended claims, which recite that the specific target fermentation product is riboflavin.

Moreover, a proper written description analysis requires an analysis of the understanding of an ordinarily skilled artisan at the time of the invention. *See* MPEP § 2163(II)(A)(2); *see also Wang Labs. v. Toshiba Corp.*, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993). As noted above, the specification provides ample information on the structures of biotin auxotrophs and how to identify them. (*See, e.g.,* Specification at pages 11-18 and Examples 1-3). And, the Examiner has conceded that the methods for making recombinant riboflavin were known, that the biosynthetic pathway of riboflavin was known, and how to make auxotrophs was known. In view of the foregoing, it is respectfully submitted that the Applicants were in possession of the full scope of the instantly claimed invention at the time the application was filed.

Accordingly, it is respectfully submitted that the rejection should be withdrawn.

For the reasons set forth above, entry of the amendments, withdrawal of all rejections, and allowance of all claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on February 26, 2007.

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